Interpretable Graph Neural Networks for Predicting the Functional State of Protein Kinases

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Overview

Elucidating the protein structure-function relationship is important in drug discovery and protein design

- We develop deep learning models based on graph neural networks (GNN) to classify the catalytically active and inactive state of protein kinases
- Interpretability of the model classification arrived from graph Grad-CAM
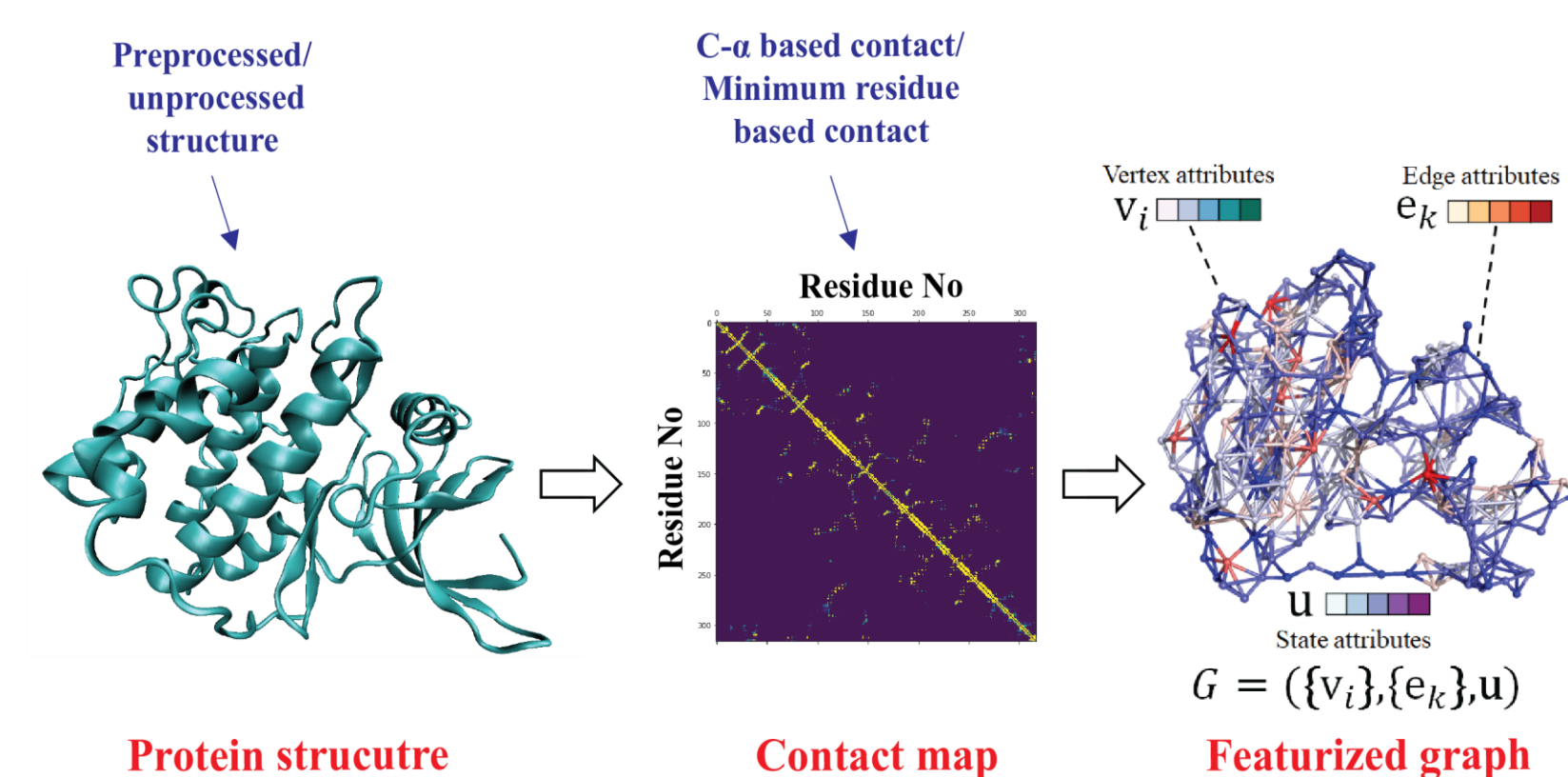
Input ⟶ Protein sequence and 3D structure

Key Takeaways

High accuracy classification of protein structures; insights into functionally important motifs without any a priori input
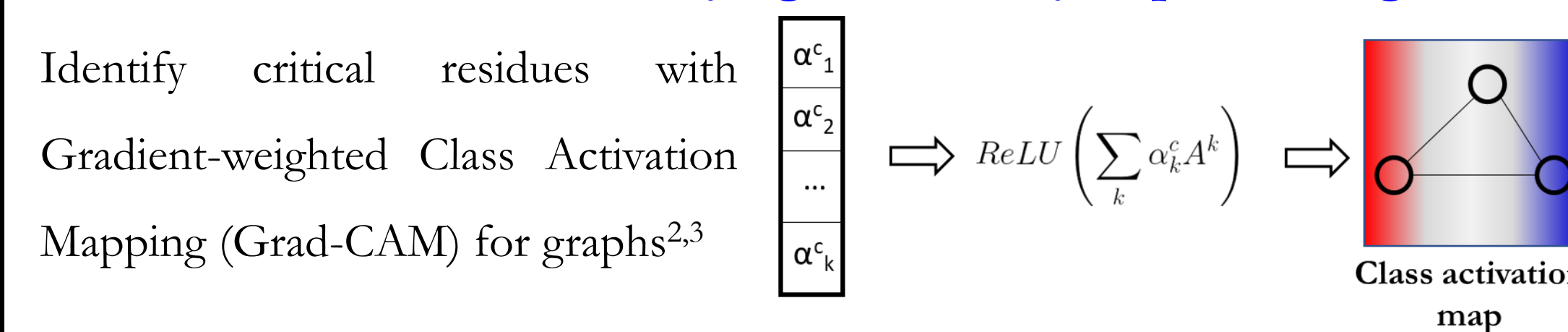
Methods

GNN for predicting the functional state of kinases
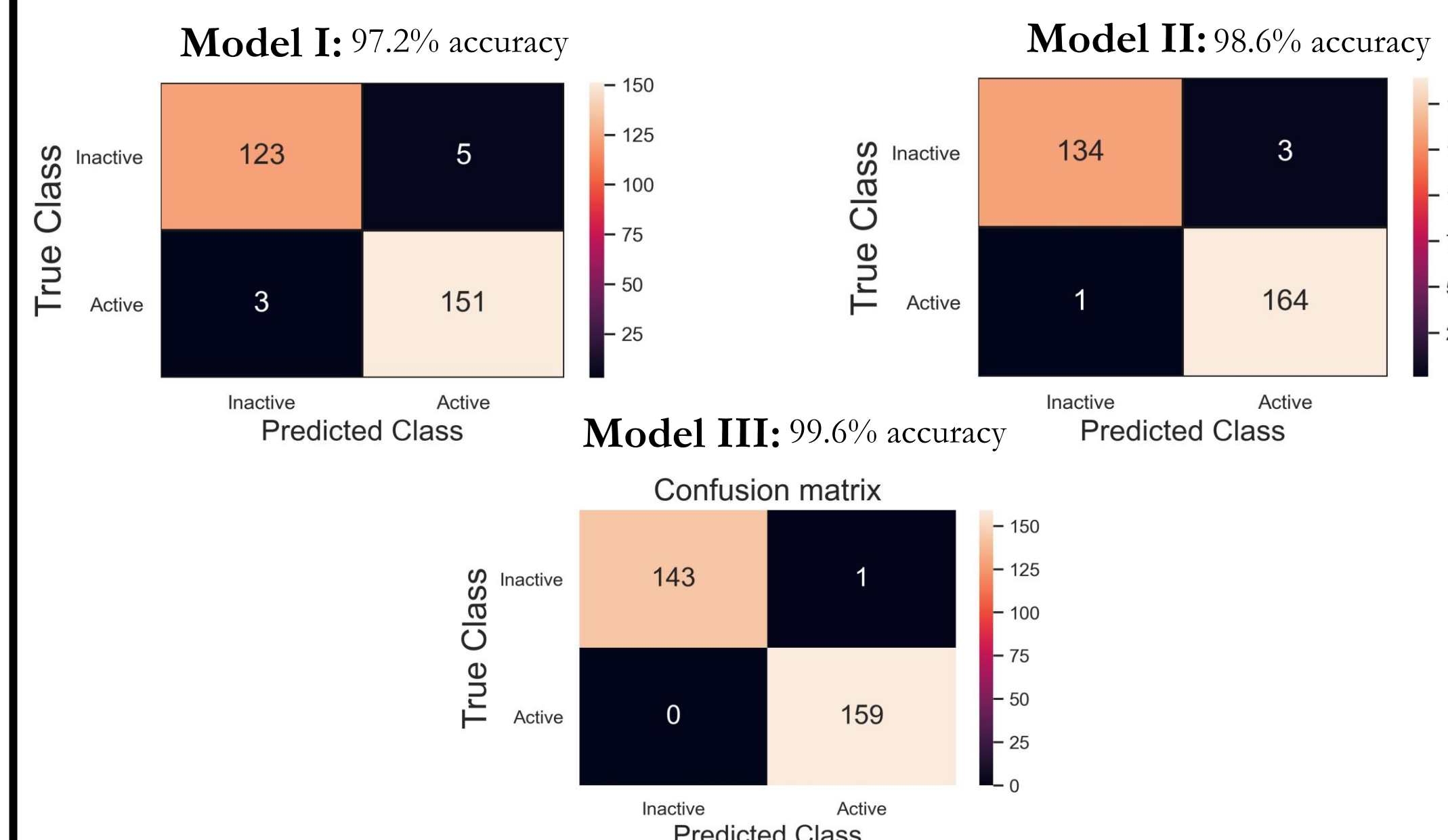
Around 3000 kinase structures obtained from PDB

Preprocessed/unprocessed structure
C-α based contact/ Minimum residue based contact
Vertex attributes v_i
Edge attributes e_k
Residue No
State attributes
u
$G = (\{v_i\}, \{e_k\}, u)$

Protein structure   Contact map   Featurized graph

MEGNet based graph architecture[1]

Grad-CAM for identifying structurally important regions

Identify critical residues with Gradient-weighted Class Activation Mapping (Grad-CAM) for graphs[2,3]

$$\begin{pmatrix} \alpha^c_1 \\ \alpha^c_2 \\ \dots \\ \alpha^c_k \end{pmatrix} \Rightarrow ReLU\left(\sum_k \alpha^c_k A^k\right) \Rightarrow$$

Class activation map

[1]Chen et al., *Chem. Mater.* (2019); [2]Selvaraju et al., *ICCV* (2017); [3]Pope et al., *CVPR* (2019).

Model Prediction

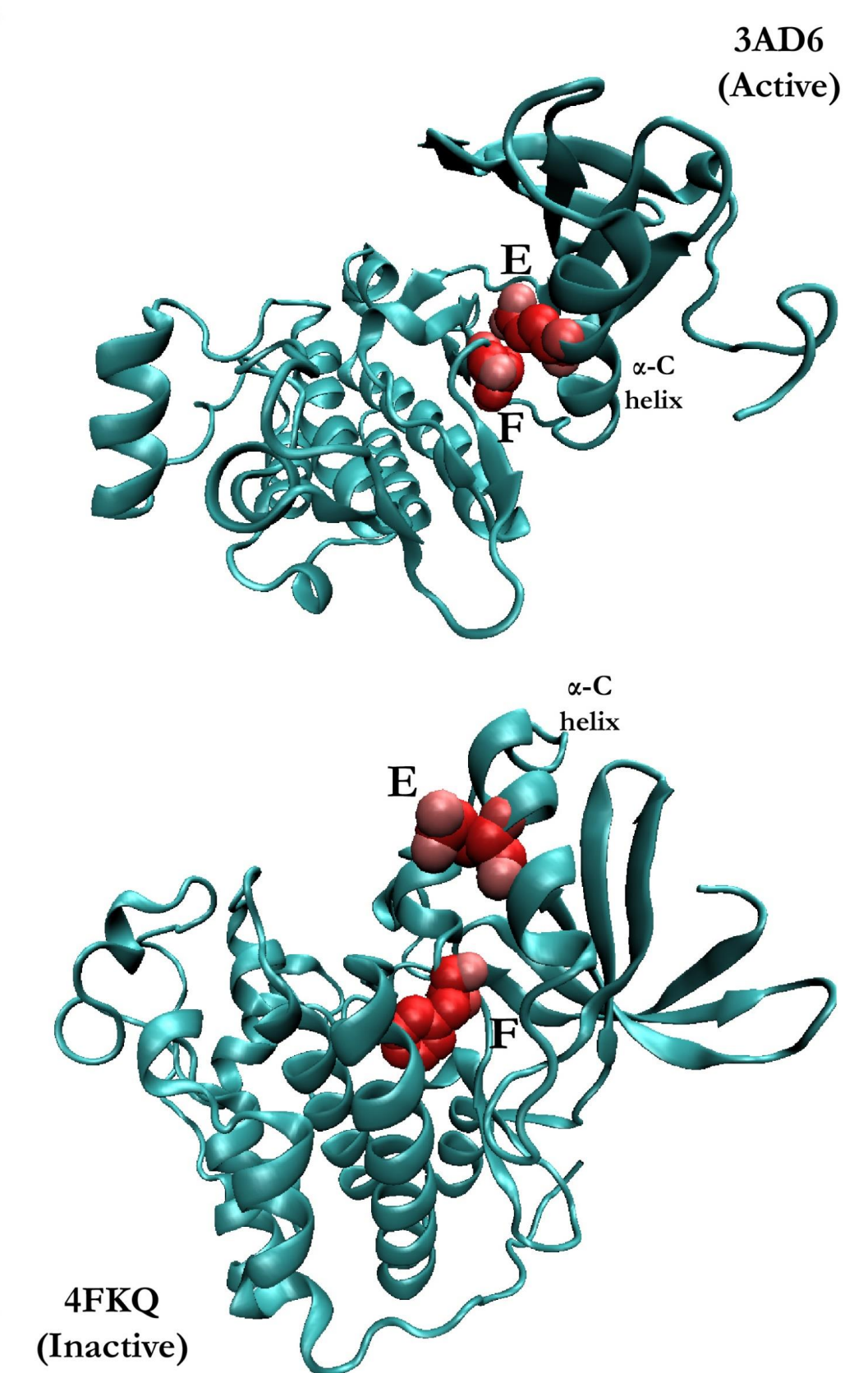**Models predict kinase functional states with high accuracy**

Model I: 97.2% accuracy

True Class	Predicted Class	
	Inactive	Active
Inactive	123	5
Active	3	151

Model II: 98.6% accuracy

True Class	Predicted Class	
	Inactive	Active
Inactive	134	3
Active	1	164

Model III: 99.6% accuracy

Confusion matrix

True Class	Predicted Class	
	Inactive	Active
Inactive	143	1
Active	0	159

Structural Analysis Based on Class Activation Maps

Residue Importance Map

High node weight
Low node weight
Non-zero edge weight
Zero edge weight
Fraction
Inactive   Active

Critical Residue-Residue Contacts

3AD6 (Active)
α-C helix
E
F

4FKQ (Inactive)
α-C helix
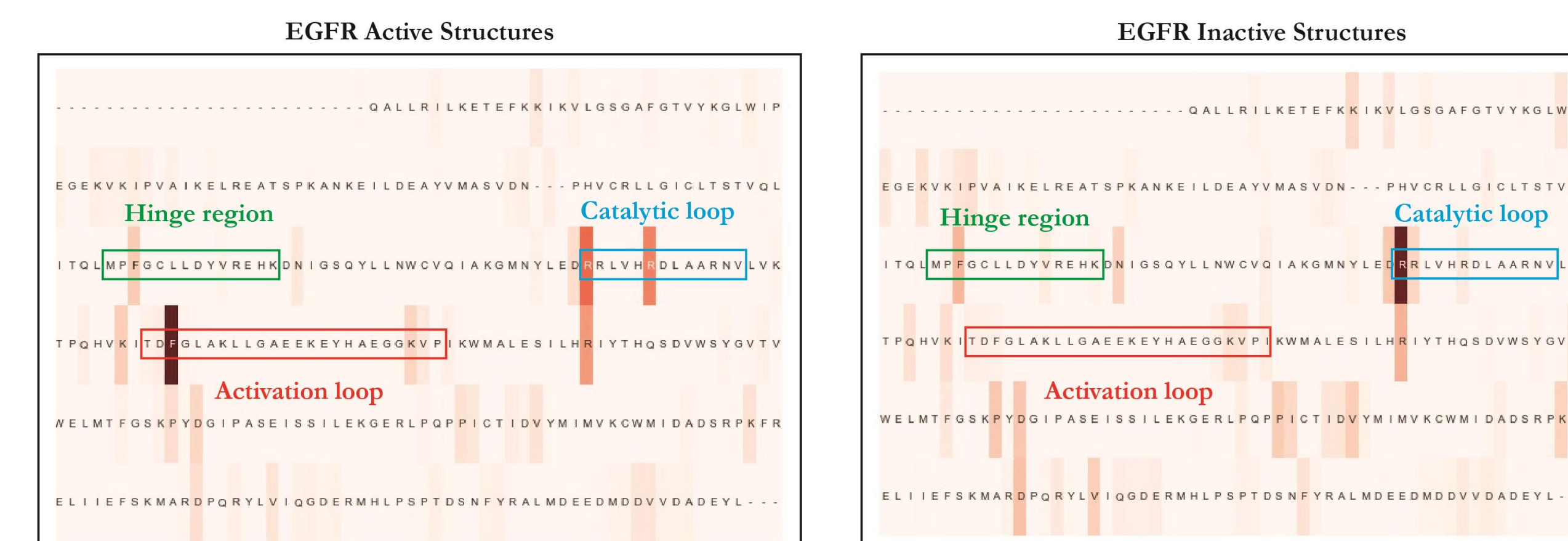E
F
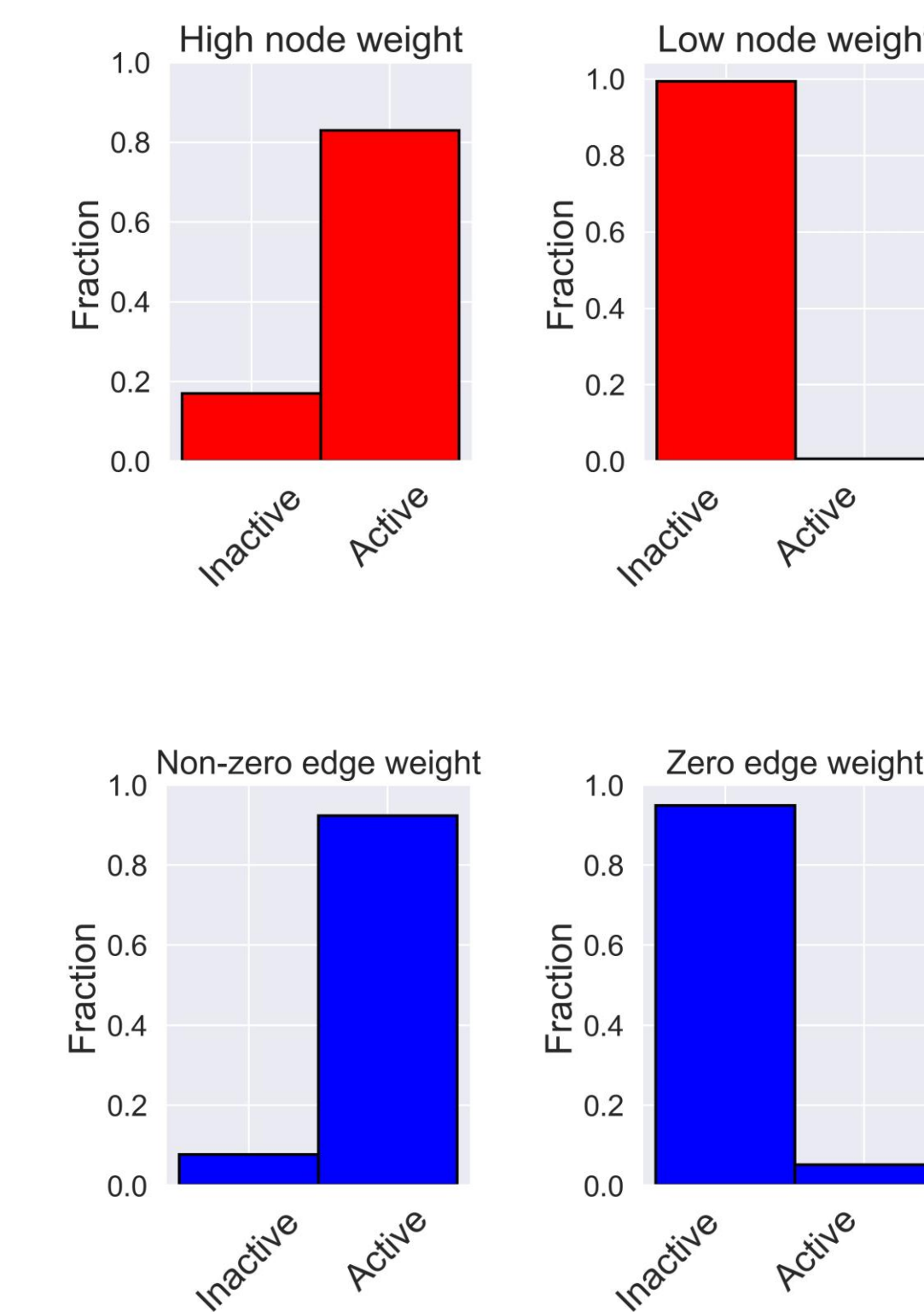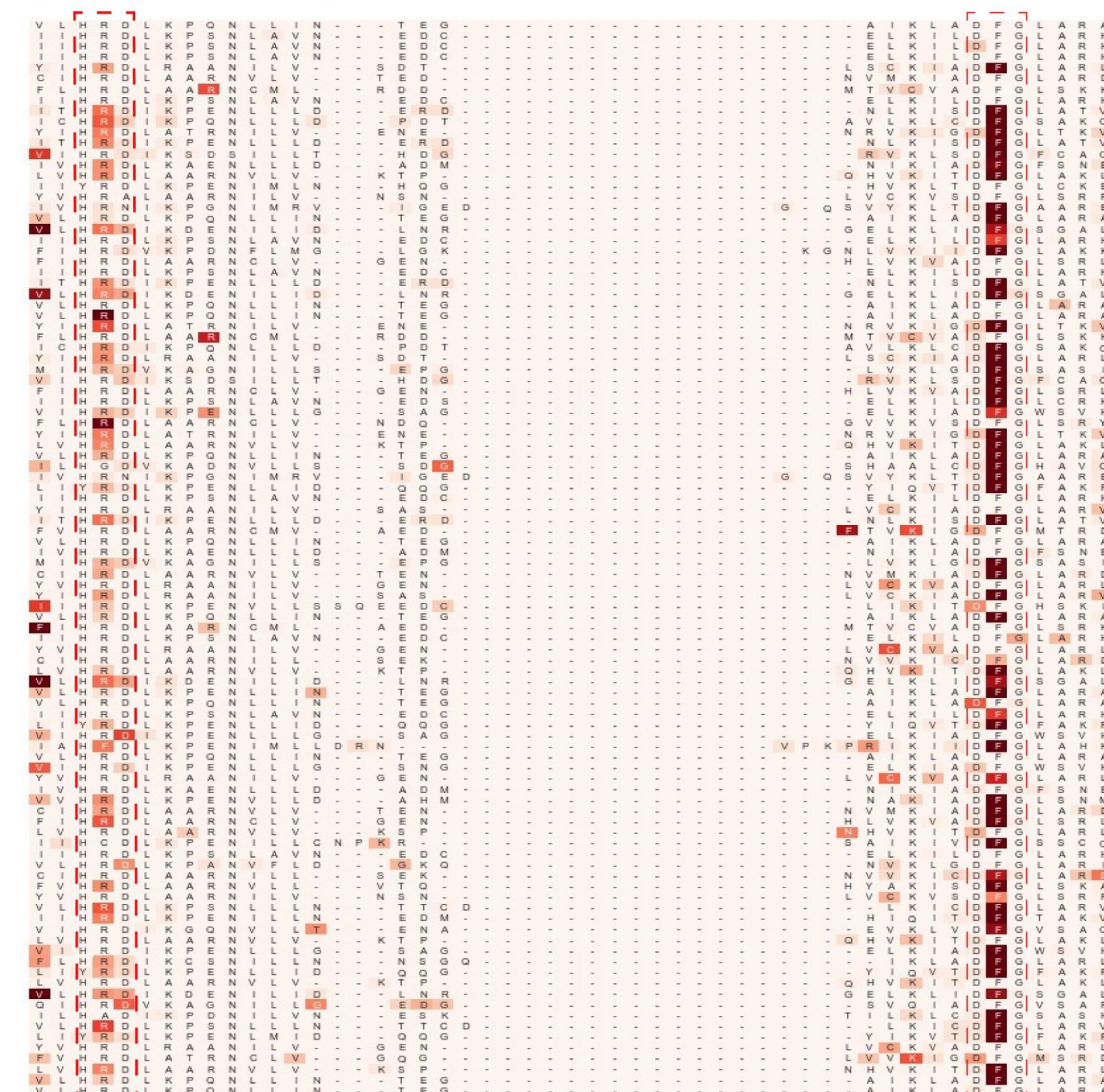
Identifying Lesser-known Residues

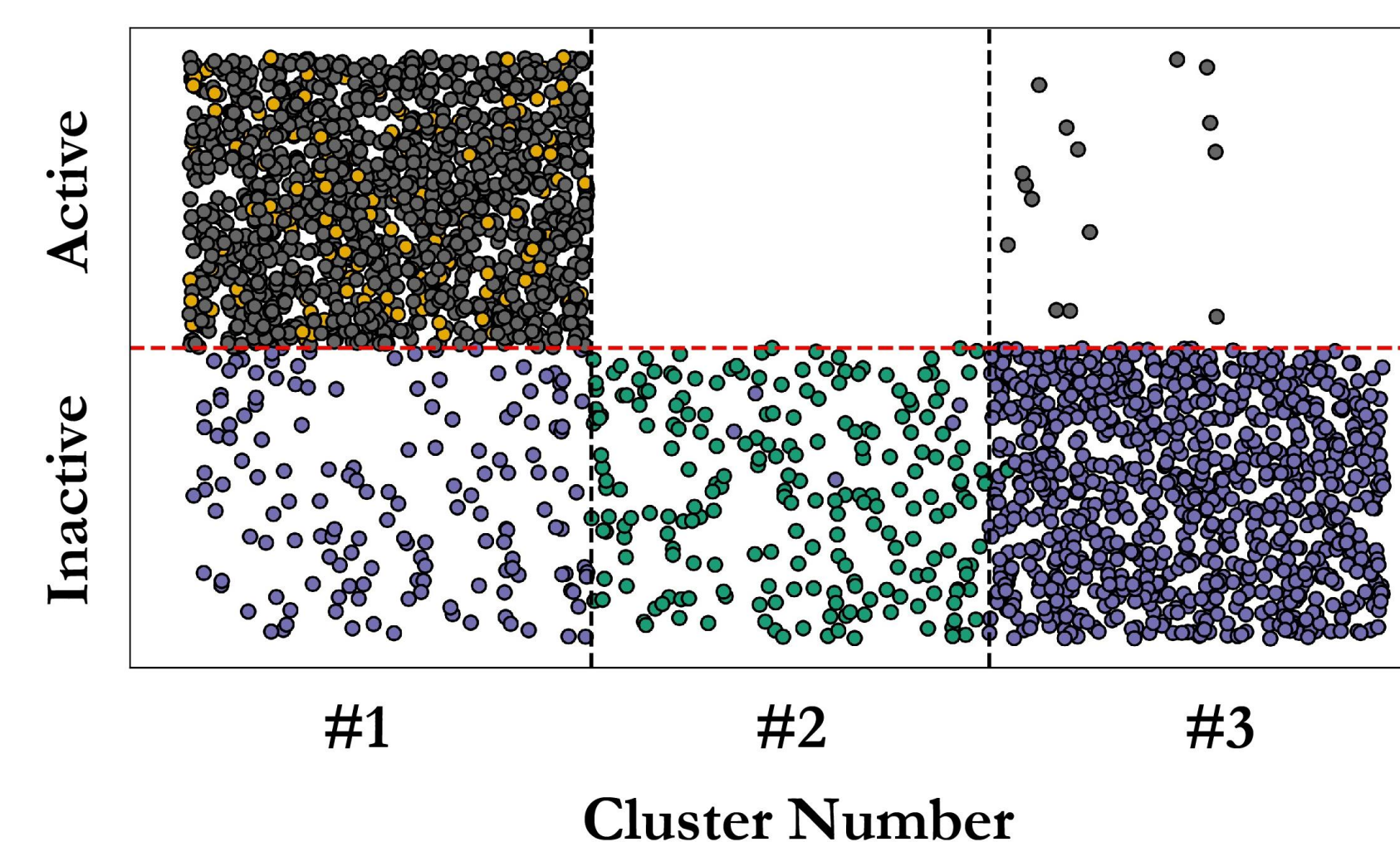Well known motifs such as the DFG (activation loop) and HRD (catalytic loop) are highlighted by Grad-CAM

Important lesser-known regions – such as the hinge region are also consistently identified

EGFR Active Structures

EGFR Inactive Structures

Hinge region   Catalytic loop

Activation loop

GNN model learns the critical residue-residue contacts that are necessary for catalytic activity (along the hydrophobic spine[4,5])

[4]Kornev et al., *PNAS* (2006); McSkimming et al., *BMC Bioinform* (2017)

Interpretable GNN framework automatically identifies structurally important motifs

Active
Inactive
Cluster Number
#1   #2   #3

Active - CDK2
Active - Rest
Inactive - CDK2
Inactive - Rest

α-C tilt (deg)
Inactive-CDK2   Inactive-Rest   Active-CDK2   Active-Rest

GNN classifies subtle structural differences in the crystal structure between sub-class of kinases